REMARKS

Claims 14 and 40 remain before the Examiner for reconsideration. Claims 1-13 and 15-39 have been canceled without prejudice. New claims 41 through 52 have been added for consideration.

In the Office Action dated January 23, 2006, the Examiner indicated: The Examiner rejected Claims 14 and 40 under 35 U.S.C. 112, first paragraph, "as failing to comply with the enablement requirement." Specifically, the Examiner asserted that:

> Applicants have narrowed the claims to just two species, which were the two recited previously in claim 39. Applicants have broadened claim 14 to embrace all cancers.
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> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
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> Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck,* 20 USPQ2d 1438, 1444. The analysis is as follows:
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> (1) Breadth of claims.
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> (a) Scope of the compounds. Two species are covered.
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> (b) Scope of the diseases covered. The coverage is immense. There are hundreds and hundreds of diverse cancers, which exist in all parts of the body. Some examples:
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> A. Melanoma is a general type of cancer, arising from cells which produce melanin, and again is distributed fairly widely in the body, including the regional lymph nodes, skin, liver, lungs, eye, brain, and mucous membranes of the genitalia, anus, oral cavity and other sites. As an example, malignant Melanoma is a malignancy of melanocytes, and occurs most commonly in the skin, but can also appear beneath the nail plate, in the eyes, ears, GI tract, leptomeninges of the central nervous system, and oral and genital mucous membranes. There are 4 major types: superficial spreading, nodular, lentigo maligna, and acral lentiginous melanoma. There are a number of uncommon forms as well: Desmoplastic/neurotropic melanoma, Mucosal (lentiginous) melanoma, Malignant blue nevus, Melanoma arising in a giant congenital nevus, and Melanoma of soft parts (a kind of clear cell sarcoma). In addition, there are Amelanotic melanomas, which are nonpigmented.
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> B. There are several main types of stomach cancers, which are very different from each other. (1) Lymphomas of the stomach are cancers of the immune system tissue that are found in the wall of the stomach. These come in two main categories. One is the Non-Hodgkin's lymphomas of the stomach, including MALT lymphoma, and assorted Large

Cell Lymphoma of the Stomach such as anaplastic CD30 (Ki- 1) positive large cell lymphoma (ALCL). The other is Hodgkin Lymphoma in the Stomach. These include both lymphomas which are primary to the stomach, and nodal lymphomas that have spread to the stomach from e.g. the spleen or liver and are thus secondary. There are Tertiary gastric lymphomas as well. (2) Gastric stromal tumors (GISTs) develop from the tissue of the stomach wall. There are an assortments of these; GISTs vary from cellular spindle cell tumors to epithelioid and pleomorphic ones. (3) Carcinoid tumors are tumors of hormone-producing cells of the stomach. These are classified into are classified into those that are associated with hypergastrinemic states (type 1, atrophic gastritis, pernicious anemia); Zollinger-Ellison syndrome [ZES] tumors (type 2), and tumors without hypergastrinemia (type 3 or sporadic). (4) Carcinoma of the Stomach exists in five types: papillary, tubular, mucinous, signet-ring cell adenocarcinoma and undifferentiated carcinoma. (5) Soft tissue sarcomas, most notably leiomyosarcoma of the stomach. There are other tumors as well, including Gastric Lipoma, gastric xanthelasma, and benign reactive lymphoid hyperplasia (pseudolymphoma).

C. There are many types of colon cancers, and this category is rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas, sarcomas (including fibrosarcomas and Leiomyosarcomas), and Carcinoid tumors. Because these are fundamentally different types of tumors, their treatment greatly differs, although adenocarcinomas and squamous cell tend to be treated the same.

D. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias, acute promyelocytic leukemias, acute myelomonocytic leukemia, chronic myelomonocytic leukemia, acute monocytic leukemias, and erythroleukemias. There is also acute megakaryoblastic leukemia, acute promyelocytic leukemia, Multiple Myeloma, lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-BCE-myeloid leukemia, acute basophilic leukemia, and acute myleofibrosis. Chromic leukemias include chronic lymphocytic leukemia(CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia(CLL), large granular lymphocytic leukemia (LGLL, which goes under several other names as well), chronic myelogenous leukemia(CML), chronic myelomonocytic leukemia, chronic granulocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia and many others.

E. The main types of lung cancer are small cell (oat cell), Giant Cell Carcinoma, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, mesothelioma and Large Cell Carcinoma (a default category of any lung tumor that cannot be otherwise classified).

F. CNS cancers cover a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. These include astrocytic tumors (e.g. astrocytomas and glioblastoma multiform) oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus,

neuronal and mixed neuronal-glial tumors (e.g. gangliocytoma, gangliogliomas, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, retinoblastoma, ependymoblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningothelial cells, including Meningiomas (including fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid, lymphoplasmacyte-rich, and metaplastic subtypes) and others such as papillary anaplastic meningioma. The category also includes non-meningothelial tumors of the meninges. Examples are benign mesenchymal tumors (e.g. osteocartilaginous tumors), malignant mesenchymal tumors (e.g. chondrosarcoma, hemangiopericytoma, rhabdomyosarcoma and meningeal sarcomatosis) primary pelanocytic Lesions (e.g. diffuse melanosis, melanocytoma), hemopoietic neoplasms (e.g. plasmactoma). A third Division are the tumors of Cranial and Spinal Nerves. This includes schwannomas, neurofibroma, and malignant peripheral nerve sheath tumor (MPNST). A fourth division are Germ Cell Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma and craniopharyngioma. Yet another division are local extensions from regional tumors, including paraganglioma, chodroma, chordoma, and chondrosarcoma. And there are many, many others.

G. Included also are bone tumors, including Osteosarcomas (osteoblastic, chondroblastic, fibroblastic, telangiectatic, and others), Hemangiosarcoma, Periosteal chondrosarcoma, Periosteal fibrosarcoma, Maxillary fibrosarcoma, Parosteal osteosarcoma, Periosteal osteosarcoma, Malignant mesenchymoma, Liposarcoma, synovial sarcoma, Osteochondroma, Hemangioma, Myxoma of the jaw, Ossifying fibroma, Osteoma, Giant cell tumor of bone, multiple myeloma, solitary myeloma, reticulum cell sarcoma, malignant fibrous histiocytoma, desmoblastic fibroma of the bone, periosteal fibroma, lipoma, Hemangioendothelial sarcoma, Ewing's sarcoma, chondroblastoma, and Multilobular tumor of bone. There are also secondary malignant deposits in bone.

H. Thyroid cancer comes in four forms: papillary thyroid cancer, follicular thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer. Of these, only one (anaplastic thyroid cancer) can be treated with anticancer agents. The other are treated with radioactivity, surgery, or thyroid suppression hormones.

I. Prostate Cancer ranges over a very wide variety of cancer types. It embraces various adenocarcinomas of the prostate, including Prostatic Ductal Adenocarcinoma, adenocarcinoma with Paneth-like cells, Clear cell adenocarcinoma, Foamy gland adenocarcinoma, Adenocarcinoma of Cowper's glands, and Atrophic adenocarcinoma. It includes a huge variety of carcinomas, including s mucinous carcinomas of the prostate, Prostatic carcinoma of xanthomatous type, signet ring cell carcinoma of the prostate, neuroendocrine small cell carcinoma of the prostate, and other small cell carcinomas of the prostate, Adenosquamous And Squamous Cell Carcinomas, Basaloid And Adenoid Cystic Carcinoma, Sarcomatoid carcinoma of the prostate, Lymphoepithelioma-like Carcinoma of the prostate, Urothelial (transitional Cell) Carcinoma (which can be primary in the prostate gland or represent secondary spread from the urinary bladder), Basaloid carcinoma, pseudohyperplastic carcinoma, and Primary carcinoma of the Seminal vesicles. There are also assorted sarcomas of the prostate, including Angiosarcoma, Embryonal rhabdomyosarcoma, Stromal sarcoma, Synovial sarcoma, Leiomyosarcoma, and chondrosarcoma of the prostate, which can be primary or secondary to the prostate. Also included is prostatic intraepithelial neoplasia (PIN), Phyllodes Tumor of the Prostate, Primitive peripheral neuroectodermal tumor (PNET) and Malignant fibrous histiocytoma. There are also lymphomas, which are usually

secondary, but primary ones include Diffuse Large B-cell Lymphoma. The great majority of the above list are not treatable with pharmaceuticals.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In iv Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is deficient. The daily dosage range information was omitted from the specification.

(4) State of the Prior Art: The claimed compounds are camptothecins. No camptothecin has ever been found to be effective against cancer generally.

(5) Working Examples: No actual working examples for the treatment of cancer are presented. Data appears for 3 cell lines. However, one cell line cannot possible demonstrate leukemia generally, and one cannot demonstrate lung generally, given the huge diversity of leukemias and lung cancers.

(6) Skill of those in the art: The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect just a single organ are often not generally treatable. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. One skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. No compound has ever been found effective generally against leukemias, lung cancers, melanomas, etc because they are simply too diverse. Lymphomas of the stomach are not commonly treated with ordinary anti-cancer agents, but instead, surgery or radiation or antibiotic therapy(e.g. amoxicillin, metronidazole, bismuth, omeprazole) are the Primary Treatments. Treatment of malignant melanoma is normally with surgery or biological agents. Chemotherapy with non-biologics has a very limited role. The great majority of prostate cancers are not treatable with pharmaceuticals. Indeed, he majority of common cancers do not respond to chemotherapy.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1 and 6, the quantity of experimentation needed is expected to be great.

> MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright,* 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.
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> The traverse is unpersuasive. Applicants had previously made a broad statement about what "camptothecin analogs" do, but this is simply not true in terms of the actual scope of this claim. Where is there evidence for example that such compounds are effective against e.g. lymphomas of the stomach, squamous cell cancer of the colon, hairy cell leukemia , or mesothelioma of the lung? With regard to the dosage, applicants point to page 10, but this simply gives the size of a dose, not a daily or weekly dosage. Thus, one does not know whether this dose is to be given, say, once a week or given e.g. 4 times a day. Applicants refer in this regard to FDA approval, but the PTO is not concerned with that; merely with what the specification actually teaches.
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> Applicants now state that 'the claims as amended set forth the subject matter of claims 39 and 40 that the examiner indicated to be allowable". This is not so. Claims 39-40 were compound claims, these are method claims.

Applicants respectfully traverse the Examiner's rejection.

As recognized by the Examiner in reviewing the factors set forth in *In re Wands*, with respect to the breadth of the claims, Applicants have set forth narrowly only two species in the claims. With respect to the diseases covered, Applicants have amended claim 14 to set forth treatment of a patient with a solid tumor cancer selected from the group consisting of malignant melanoma, stomach cancer, breast cancer, ovarian cancer, lung cancer, and colorectal cancer or leukemia. Further Applicants have added new independent claim 43 setting forth a method of treating a patient with a solid tumor cancer, comprising the step of administering a pharmaceutically effective amount of a compound of 7-trimethylsilyl-10-hydroxy camptothecin or 7-tert-butyldimethylsilyl-10-hydroxy camptothecin. Contrary to the Examiner's assertions the camptothecin (CPT) class of compounds (for which, a molecular target has been established to be human DNA topoisomerase I or topo I) has been demonstrated to be effective against a broad spectrum of tumors and leukemia. Indeed, numerous review articles set forth the broad-spectrum activity of the camptothecin family of compounds. Such broad-spectrum activity has also been set forth in the patent literature. See, for example, U.S. Patent Nos. 6,242,457, 6,509,345 and 6,699,876.

Moreover, the United States Patent and Trademark Office has recognized the broad-spectrum activity of the camptothecin class of family of compounds by issuing

numerous US Patents claiming a method of treatment of cancer/leukemia patients with camptothecin and/or analogs thereof. See, for example, U.S. Patent No. 5,340,817 (setting forth a method of treating a colon tumor, a rectal tumor or leukemia) and U.S. Patent No. 6,624.170 (setting forth a method treating or retarding a malignant tumor, wherein the malignant tumor is selected from the group consisting of breast cancer, lung cancer, stomach cancer, ovarian cancer, pancreas cancer, prostate cancer, osteosarcoma, melanoma and bladder cancer). Many more examples can be set forth.

With respect to the state of the prior art, as set forth above, the camptothecin class of compounds is know to have activity/effectiveness against a broad spectrum of solid tumor cancers and leukemia.

With respect to the skill of those in the art, Applicants respectfully assert that the level of such skill is very high, on the level of a doctorate degree or degrees in, for example, medicine, chemistry, pharmacology etc.

With respect to the predictability in the art, once again the camptothecin class of compound is known to have activity/effectiveness against a broad spectrum of solid tumor cancers (for example, those set forth in claim 14) and leukemia. The United States Patent Office has recognized repeatedly, this broad spectrum of activity. The compounds of the present invention were shown to exhibit good to excellent antitumor activity as compared to, for example, the broadly active compounds camptothecin (CPT) and the camptothecin analog irinotecan (IRT). The camptothecin derivatives of the present invention were, for example, evaluated for their cytotoxic effects on the growth of HL-6O (human promyelocytic leukemic), 833K (human teratocarcinoma) and/or DC-3F (hamster lung) cells *in vitro* and/or for antitumor activity in $B_6D_2F_1$ mice bearing sarcoma-180 or Lewis lung murine solid tumor. Potency in enhancing the DNA-topoisomerase I-mediated cleavage of PBR_{322} DNA, or in inhibiting the DNA-topoisomerase I-mediated relaxation of PBR_{322} DNA was also evaluated. Given known structure activity relationships of camptothecin compounds, one skilled in the art is readily apprised of the broad-spectrum activity of the compounds used in the present methods of treatment. The present inventors have demonstrated that introduction of a

silyl group (for example, a trimethylsilyl group or a tert-butyldimethylsilyl group) at position 7 of the camptothecin structure provides compounds with generally better anti-tumor activity than camptothecin This activity remained essentially unchanged when a hydroxy group was introduced at position 10 of the compound. In this context, the methods of treatment of the present invention set forth camptothecin analogs that combine good to excellent anti-tumor activities with advantageous solubility and biodistribution profiles.

With respect to the amount of direction provided by the inventors in regard to the existence of working examples (dosages) and the quantity of experimentation needed to make or use the invention, in addition to the remarks set forth above, Applicants have set forth in the specification that:

> The present invention also provides a method of treating a patient, which comprises administering a pharmaceutically effective amount of a compound of formula (1) or a pharmaceutically acceptable salt thereof. The compound may, for example, be administered to a patient afflicted with cancer and/or leukemia by any conventional route of administration, including, but not limited to, intravenously, intramuscularly, orally, subcutaneously, intratumorally, intradermally, and parenterally. The pharmaceutically effective amount or dosage is preferably between 0.01 to 60 mg of the compound of formula (1) per kg of body weight. More preferably, the pharmaceutically effective amount or dosage is preferably between 0.1 to 40 mg of the compound of formula (1) per kg of body weight. In general, a pharmaceutically effective amount or dosage contains an amount of a compound of formula (1) effective to display antileukemic and/or antitumor (anticancer) behavior. Pharmaceutical compositions containing as an active ingredient a compound of formula (1) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier or diluent are also within the scope of the present invention.
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> The compounds of the present invention can be administered in a variety of dosage forms including, for example: parenterally (for example, intravenously, intradermally, intramuscularly or subcutaneously); orally (for example, in the form of tablets, lozengers, capsules, suspensions or liquid solutions); rectally or vaginally, in the form of a suppository; or topically (for example, as a paste, cream, gel or lotion).

> Optimal dosages to be administered may be determined by those skilled in the art and will vary with the particular compound of formula (1) to be used, the strength of the preparation, the mode of administration, the time and frequency of administration, and the advancement of the patient's condition. Additional factors depending on the particular patient will result in the need to adjust dosages. Such factors include patient age, weight, gender and diet. Dosages may be administered at once or divided into a number of smaller doses administered at varying intervals of time.

(p. 10, and pp. 22-23). Given the very high level of skill of those skilled in the art, the established activity of the compounds set forth in the claims of the present invention, and the extent of guidance provided by the prior art in setting forth treatment protocols for camptothecin analogs similar in activity to the present invention, Applicants respectfully assert that no undue experimentation is required to make use of the method of treatment of the present invention.

In view of the above amendments and remarks, the Applicants respectfully requests that the Examiner, indicate the allowability of the Claims, and arrange for an official Notice of Allowance to be issued in due course.

Respectfully submitted,

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